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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 04/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/834,109	SEGAL ET AL.	
	Examiner	Art Unit	
	Jehanne Souaya Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *2,11 and 15* is/are allowed.

6)☒ Claim(s) *1,3-10,12-14,16-19 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The examiner reviewing your application at the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to examiner Jehanne Sitton.

2. Currently, claims 1-19 and 22 are pending in the instant application. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections are either newly applied or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is NON-FINAL.

3. The rejections set forth in section 6 of the previous office action are withdrawn. Sections 6a, c, and d are withdrawn in view of the amendments to the claims. Section 6b is withdrawn in view of the new ground of rejection.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Maintained Rejections

Claim Rejections - 35 USC § 112

5. Claim 22 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for in vitro methods of use, does not reasonably provide enablement for in vivo methods of use. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claim is drawn to a method o gene therapy wherein the nucleic acid molecule of claim 1 or 2 comprising an aptamer and a nonaptameric biological effector sequence is introduced in vitro into a host cell whereby the effector sequence is internalized and the host cell is administered to an organism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate with ex vivo gene therapy encompassed by claim 22. There is no working example or description or even a prophetic example of the claimed aptamer covalently linked to a nucleic acid sequence comprising a "biological effector sequence" which, when introduced into an organism by the claimed invention method, effects a specific biological reaction. Example: of "biological effector sequences" include coding and antisense nucleic acids, nucleic acid enzymes and regulatory nucleic acids (page 14, first paragraph, followed by lists of prospective effector sequences). Working examples (pages 30-36) are prophetic with the exception of Example 6 in which antisense effector sequences were shown to inhibit expression of Enhanced Green Fluorescent Protein in vitro to a greater degree when conjugated to a human L-selectin aptamer than the aptamer alone. The specification is primarily directed to gene therapy of animals including humans (pages 27-29). However, at the time the application was filed, the prior art taught that gene therapy and antisense therapy were inoperative at worst and unpredictable at best. For example, Orkin et al. (1995) reviewed the state of the gene therapy art and reported that, among other problems, "[e]fficacy has not been established for any gene therapy protocol". Notably, in this regard, the specification describes dosage and administration in generalities (pages 28-29) but fails to provide any specific protocol for performing the claimed invention gene therapy methods. The Orkin et al. report also cited "the low frequency of gene delivery to

target cells and the lack of definable biochemical or clinical endpoints". Notably, in this regard, the specification fails to identify any biochemical or clinical endpoints of the claimed invention methods. Administration of antisense oligonucleotides has been shown to have unexpected effects as reported in Science (Gura 1995). In one example wherein inhibition of B cell activity in culture was attempted the antisense oligonucleotides instead increased B cell activity. This report also cited side effects in animals administered antisense oligonucleotides including death in some instances. While the level of skill in the molecular biology art was high at the time of the claimed invention, Ph.D. or higher, the level of unpredictability was also high as demonstrated by the cited references. Absent the required teaching and/or guidance in the specification, it is clear that the skilled practitioner in the art would have experienced undue experimentation in attempting to practice the claimed invention method of gene therapy comprising "introducing a biological effector sequence into a cell" and "administering said host cell to an organism" and that the disclosure is nothing more than an invitation to experiment. As the Courts have stated,

> A specification must be more than an invitation to experiment, i.e., applicant may not require persons skilled in the art to perform undue experimentation to achieve a successful result, See In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1933); In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Response to Arguments

6. The response traverses the rejection. The response asserts that because applicant has taught how to make the nucleic acid/aptamer molecules of the invention, how to introduce the molecule into a cell and test for introduction, and how to introduce the cell into an organism, applicant has met the burden of enablement. This argument has been thoroughly reviewed but

was found unpersuasive. As the response has acknowledged, the enablement requirement stipulates that applicants must teach how to make and use the claimed invention without undue experimentation. However, the sections in the specification relied upon in the response are how to make the in vitro aspects of the invention. In the previous office action, the examiner set forth the reasons why applicant had not enabled in vivo methods. However, the specification set forth that the use for the method of claim 22 is gene therapy, which is not enabled by the specification for the reasons set forth above and in the previous office action. Therefore, for these reasons and the reasons set forth in the previous office action, the rejection is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

7. Claims 3-6 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3-6 are indefinite. In claims 3 and 4, the claims recite that a third nucleic acid sequence is an aptamer. However, claims 5 and 6 recite "said third nucleic acid sequence comprises an aptamer". It is confusing if claims 5 and 6 are broader than claims 3 and 4, "comprising" vs "is" or if the nucleic acid in claims 3 and 5 or claims 4 and 6 are the same. Accordingly, in claims 5 and 6 it is also confusing if the claim is setting forth that the aptamer that is the third nucleic acid sequence is different than the first nucleic acid sequence and therefore the first aptamer of claims 1 and 2 respectively, or if just the nucleic acid comprising the aptamers are different, but that the aptamers could be the same.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 1, 7, 8, 10, 13, 14, and 16-19 are rejected under 35 U.S.C. 102(e) as being anticipated by Toole et al (hereinafter referred to as Toole; US Patent 5,582,981; 102(e) date: 8/14/1991).

For the purposes of this rejection, the nucleic acid comprising a biological effector sequence which is not an aptamer has been broadly interpreted to encompass a vector comprising a promoter construct covalently bonded to an aptamer.

Toole teaches aptamer nucleic acid sequences specific for a selected target, including cell surface molecules such as receptors, ion channels, or extracellular matrix molecules (see col. 3, lines 58-64). Toole teaches that aptamers function like monoclonal antibodies in their specificity and usage (see col. 4, lines 5-6). With regard to claims 1, 7, 8, 10, 13, 14, and 16-19, Toole teaches that the aptamer can be included in a suitable expression system to provide for in situ generation of the desired sequence (see col. 6, lines 19-21). The specification does not define the term biological effector sequence. The broadest reasonable interpretation of this claim includes any nucleotide sequence that has some biological effect. Such nucleic acid biological effector sequences could include vectors comprising promoter sequences or sequences with the ability to

hybridize to another nucleic acid sequence. In the instant case, the expression system taught by Toole is an inherent teaching of a cell comprising a vector/promoter complex for in situ generation of the aptamer and therefore the biological effector sequence is inherently covalently bonded to the aptamer.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1, 7-10, 13, 14, and 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Toole in view of Hirsch et al (hereinafter referred to as Hirsch; US Patent 5,428,132).

For the purposes of this rejection, the nucleic acid comprising a biological effector sequence which is not an aptamer has been broadly interpreted to encompass a nucleic acid that encodes a protein.

Toole teaches aptamer nucleic acid sequences specific for a selected target, including cell surface molecules such as receptors, ion channels, or extracellular matrix molecules (see col. 3, lines 58-64). Toole teaches that aptamers function like monoclonal antibodies in their specificity and usage (see col. 4, lines 5-6). Toole teaches that the aptamers can be used in therapeutic applications for transmucosal, transdermal or oral administration (see col. 10, lines 31-67). Toole also teaches that aptamers can be employed in expression systems in applying gene

therapy. Although Toole does not teach making a specific construct comprising an aptamer and a nucleic acid encoding a protein with a biological effect, Hirsch teaches a construct comprising an antibody, which is used for targeting a specific cell type - for example an antibody that binds a surface antigen of a cell into which a nucleic acid needs to be integrated, covalently or non covalently linked to a nucleic acid that encodes a protein wherein the nucleic acid is to be integrated into a cell for the purposes of expressing the protein inside the cell (see col. 1,lines 57-col. 2, line 21). Hirsch specifically teaches a method of using this construct to transfect DNA into cells that then express the protein encoded by the DNA (see col. 3). Hirsch specifically teaches that this method can be used for incorporating genes into cells (see col. 4). Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody in the construct of Hirsch with the aptamer of Toole because Toole teaches making therapeutic constructs comprising aptamers linked to nucleic acids for delivery of nucleic acids into cells. The ordinary skilled artisan would have had a reasonable expectation of success that the antibody of Hirsch could be substituted with the aptamer of Toole for delivery of nucleic acids into cells because Toole specifically teaches that aptamers function like antibodies in their specificity and usage and Hirsch teaches the successful delivery of nucleic acid into a cell using an antibody and subsequent stable expression.

12. Claims 1 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Toole in view of George et al (hereinafter referred to as George; US Patent, 5,741,679).

Toole teaches aptamer nucleic acid sequences specific for a selected target, including cell surface molecules such as receptors, ion channels, or extracellular matrix molecules (see col. 3, lines 58-64). Toole teaches that aptamers can be DNA or RNA and derivatized to include

enzymatic activities which perform a desired function at a target site (see col. 6, lines18-19). Toole does not teach an aptamer linked to a ribozyme. However, George teaches a regulatable ribozyme which comprises an RNA sequence which binds a ligand (which can be a protein) linked to a ribozyme (a nucleic acid enzyme). The RNA sequence which binds a ligand is an aptamer (see col. 6 which teaches how to select for random RNA sequences which specifically bind a ligand; claims 1-28). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the derivatized aptamer of Toole to include a ribozyme linked to the aptamer because Toole teaches derivatizing the aptamers taught by Toole (which specifically bind target such as cell surface molecules) to include enzymatic activities. The ordinary artisan would have been motivated to derivatize the aptamer of Toole with a ribozyme because George teaches making a regulatable ribozyme which is under the control of the ligand binding RNA sequence which binds a target. Making such a construct would have made the aptamers of both Toole and George more versatile. The ordinary artisan would have had a reasonable expectation of success that an aptamer could be covalently bound to a ribozyme because George teaches making a ribozyme which is covalently bound to an aptamer.

Conclusion

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (571) 272-0507.

Jehanne Sitton

Jehanne Sitton
Primary Examiner
Art Unit 1634

4/5/04